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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/386,450	08/31/1999	GERTRUD HOTTEN	P564-9022	1400

7590 05/20/2002

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	PAPER NUMBER
1647	19

DATE MAILED: 05/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

B.S

Office Action Summary	Application No. 09/386,450	Applicant(s) HOTTEN ET AL.	
	Examiner David S Romeo	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,9,11,13,16,20-22 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,9,11,13,16,20-22 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 31, 2001 (Paper No. 15) has been entered. The submission filed on December 31, 2001 (Paper No. 15) simultaneously requested canceling claim 20 and amending claim 20. The request to cancel claim 20 has not been entered and the amendment to claim 20 has been entered.

Claims 6, 9, 11, 13, 16, 20-22, 24-27 are pending and being examined. Any objection and/or rejection of record that is not maintained and/or repeated in this Office action is withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Citations by the examiner are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

The specification contains the following pertinent disclosures regarding the meaning of a "mature" protein: "The start of the mature protein begins after nucleotide 1782" (page 4, full paragraph 2), and "The region coding for the mature part of the protein extends from nucleotides 1783-2142 of the sequence shown in SEQ ID NO. 1" (paragraph bridging pages 5-6). For

patentability determination purposes, the reasonable interpretation of these pertinent disclosures is that the region coding for the mature protein begins at nucleotide 1783, and that "the" or "a" mature protein is amino acids 382 to 501 of the present application's SEQ ID NO: 2.

Maintained Formal Matters, Objections, and/or Rejections:

None.

New formal matters, objections, and/or rejections:

Claim Rejections - 35 USC § 112

The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is indefinite over the recitation of the limitation "and which has essentially the same osteoinductive activity of the protein" because it is unclear which protein is intended. The metes and bounds are not clearly set forth. This limitation does not appear to be essential, and the claim would not be objected to or rejected for the absence of this limitation.

Claim 27 is indefinite over the recitation of "dimmer" because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "dimmer". An artisan cannot determine what additional or material functional limitations are placed upon a claim by the presence of this element. It is suggested that the claims recite "dimer".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 11, 27 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee (1, cited by Applicants).

This rejection is based upon an effective filing date of January 12, 1993 for mouse and human GDF-5s.

Claim 11 is directed to or encompasses a protein of the TGF-β family encoded by a DNA molecule which comprises a nucleotide sequence which encodes a portion of the amino acid sequence according to SEQ ID NO: 2, wherein said portion comprises the amino acid sequence of SEQ ID NO: 13.

Lee discloses an isolated polynucleotide encoding GDF-5 and isolation and purification of recombinantly expressed GDF-5 (column 4, line 36, through column 7, line 47; Figures 2A-2B; SEQ ID NO: 10). Partial cDNA analysis of a human PCR product revealed no predicted

amino acid differences between mouse and human GDF-5 (column 13, lines 23-25). GDF-5 is a member of the TGF-β superfamily of proteins (paragraph bridging columns 2-3). Amino acids 394 to 495 of GDF-5 are identical to the amino acid sequence of the present application's SEQ ID NO: 13. Accordingly, Lee discloses a protein of the TGF-β family encoded by a DNA molecule which comprises a nucleotide sequence which encodes a portion of the amino acid sequence according to SEQ ID NO: 2, wherein said portion comprises the amino acid sequence of SEQ ID NO: 13. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, claimed properties or functions are presumed to be inherent, and a prima facie case of either anticipation or obviousness has been established. The proteins of the TGF-β family are initially synthesized as a large precursor protein which subsequently undergoes proteolytic cleavage at a cluster of basic residues approximately 110-140 amino acids from the C-terminus. In each case, the active species appears to be a disulfide-linked dimer of C-terminal fragments. See column 1, lines 38-57. Polynucleotide sequences encoding GDF-5 can be expressed in eukaryotes (column 7, full paragraph 1). Expression of polynucleotide sequences encoding GDF-5 in eukaryotes would result in the formation of a dimer in the absence of evidence to the contrary and because, in each case, the active species of TGF-β family members appears to be a disulfide-linked dimer of C-terminal fragments.

Claim Rejections - 35 USC § 103

Claims 9, 11, 13, 16, 20, 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee (1, cited by Applicants) as applied to claim 11 above and further in view of Oppermann (2, cited by Applicants).

Lee discloses GDF-5, as discussed above. The structural homology between the GDF-5 protein of this invention and the members of the TGF-β family, indicates that GDF-5 is a new member of the family of growth and differentiation factors. Based on the known activities of many of the other members, it can be expected that GDF-5 will also possess biological activities that will make it useful as a diagnostic and therapeutic reagent. See paragraph bridging columns 2-3. GDF-5 contains all of the highly conserved residues present in other family members, including the seven cysteine residues with their characteristic spacing. Among the known family members, GDF-5 is most highly related to BMP-2 and BMP-4 in the C-terminal portion of the molecule (57% amino acid sequence identity calculated from the first conserved cysteine). See paragraph bridging columns 4-5. The bone morphogenetic proteins (BMPs, osteogenin, OP-1) can induce de novo cartilage and bone formation (column 1, full paragraph 3). Lee is silent with respect to a pharmaceutical composition comprising GDF-5.

Oppermann discloses a bioassay for bone induction that may be used to monitor endochondral bone differentiation activity of a BMP. Bone matrix implants were assayed for bone forming activity. See paragraph bridging columns 57-58. Oppermann discloses a BMP contained on and/or in a natural or synthetically prepared matrix material that can be biologically degraded (column 49, line 20, through column 57, line 35). Oppermann's natural or

synthetically prepared matrix material is a pharmaceutically acceptable carrier, diluent or filler, or a dental implant. Oppermann does not teach GDF-5.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make GDF-5, as taught by Lee, and to modify that teaching by making GDF-5 contained on and/or in a natural or synthetically prepared matrix material, as taught by Oppermann, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to determine the bone and/or cartilage inducing activity of GDF-5. The intended uses of the claimed invention and/or pharmaceutical compositions do not result in a structural difference between the present invention and the prior art pharmaceutical compositions and do not patentably distinguish the claimed invention from the prior art. The invention is prima facie obvious over the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 6, 9, 11, 13, 16, 20-22, 24-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No.

6120760. Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims is directed to or encompasses the same polypeptide, i.e., a polypeptide comprising the amino acid sequence of the present application's mature protein.

If necessary, claims 6, 9, 11, 13, 16, 20-22, 24-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6120760 in view of Lee (1, cited by Applicants) and further in view of Oppermann (2, cited by Applicants). The pertinent teachings of Lee and Oppermann are discussed above. The composition claims of the present application are an obvious variation of the product and composition claims of the patent in view of Lee and further in view of Oppermann.

Conclusion

No claims are allowed. The closest prior art of Lee (1, cited by Applicants) does not teach or fairly suggest the present application's mature polypeptide because of the single amino acid difference between Lee's SEQ ID NO: 10 and the present application's SEQ ID NO: 2 shown in the sequence comparison below:

```
Db     355 RSGQDDKTVYEYLFSQRRKRRAPLANRQGKRPSKNLKARCSRKALHVNFKDMGWDDWIIA 414
           ||||||||||||||||||||||||| |||||||||||||||||||||||||||||||||||
Qy     361 RSGQDDKTVYEYLFSQRRKRRAPLATRQGKRPSKNLKARCSRKALHVNFKDMGWDDWIIA 420.
```

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

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FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

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DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

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DSR
MAY 18, 2002